Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
November 3, 2010

Topic: The committee discussed a number of safety concerns with intravenous administration of the anti-seizure drugs phenytoin and fosphenytoin, including the condition known as Purple Glove Syndrome (PGS), and recommended what regulatory actions, if any, are necessary to diminish the risks.

These summary minutes for the November 3, 2010 joint meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee were approved on November 23, 2010.

I certify that I attended the November 3, 2010 joint meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee and that these minutes accurately reflect what transpired.

_____*-signed-*_____
Diem-Kieu H. Ngo, Pharm.D., BCPS
(Designated Federal Official)

_____*-signed-*_____
Britt Anderson, M.D., Ph.D.
(Chair)

Summary Minutes of the Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
November 3, 2010

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee joint meeting held on November 3, 2010. A verbatim transcript will be available in approximately six weeks, sent to the Division and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm204899.htm and
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm199874.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 3, 2010, at the Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Pfizer, Inc. The meeting was called to order by Britt Anderson, M.D., Ph.D. (Chair); the conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., BCPS (Designated Federal Official). There were approximately 100 people in attendance. There was one Open Public Hearing (OPH) speaker.

Issue: The committee discussed a number of safety concerns with intravenous administration of the anti-seizure drugs phenytoin and fosphenytoin, including the condition known as Purple Glove Syndrome (PGS), and recommended what regulatory actions, if any, are necessary to diminish the risks.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee members present (voting):
Britt Anderson, M.D., Ph.D. (Chair); Nathan B. Fountain, M.D.; Samuel A. Frank, M.D. (Consumer Representative); Mark W. Green, M.D.; Pooja Khatri, M.D., FAHA; Dean D. Kindler, M.D.; Ying Lu, Ph.D.; Ellen J. Marder, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members not present (voting):
Jeffrey A. Cohen, M.D.; Jason W. Todd, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members present (non-voting):
Roy Twyman, M.D. (Industry Representative)

Drug Safety and Risk Management Advisory Committee members present (voting):
Lewis S. Nelson, M.D., FACEP, FACMT, FAACT; Sidney M. Wolfe, M.D. (Consumer Representative)

Drug Safety and Risk Management Advisory Committee members not present (voting):
Elaine H. Morrato, Dr.PH.; Allen J. Vaida, Pharm.D.

Temporary Voting Members:
Marshall S. Balish, M.D., Ph.D.**;** José E. Cavazos, M.D., Ph.D., FAAN; Kevin E. Chapman, M.D.; William O. Cooper, M.D., M.P.H.; Collin A. Hovinga, Pharm.D.; J. Stephen Huff, M.D.; Ellen F. Kandell, J.D. (Patient Representative); Michael P. Lee, Pharm.D., NCPS, BCPS; Andrew M. Naidech, M.D., MSPH; Phillip L. Pearl, M.D.; Michael A. Rogawski, M.D., Ph.D.; Steven C. Schachter, M.D.; Robert Silbergleit, M.D.; Betsy L. Sleath, Ph.D.; Wayne R. Snodgrass, M.D., Ph.D.; Brian K. Solow, M.D., FAAFP; Stacia L. Spridgen, R.Ph., Pharm.D., BCNP; Panayiotis N. Varelas, M.D., Ph.D.; T. Mark Woods, Pharm.D., FASHP, BCPS

Guest Speakers (non-voting): Thomas E. Bleck, M.D., FCCM; William M. Coplin, M.D., FCCM; Francesca E. Cunningham, Pharm.D.

FDA Participants (non-voting): Robert Temple, M.D., Russell G. Katz, M.D.; Norman Hershkowitz, M.D., Ph.D.; Mark Avigan, M.D., C.M.

Open Public Hearing Speaker: Jaideep Kapur, MBBS, Ph.D.

The agenda was as follows:

Call to Order and Opening Remarks	***Britt Anderson, M.D., Ph.D.*** *Chair* *Peripheral and Central Nervous System Drugs Advisory Committee*
Introduction of Committee	
Conflict of Interest Statement	***Diem-Kieu H. Ngo, Pharm.D., BCPS*** *Designated Federal Official*
FDA Introductory Remarks	***Russell Katz, M.D.*** *Director, Division of Neurology Products (DNP), Office of Drug Evaluation I, Office of New Drugs (OND), CDER, FDA*
FDA PRESENTATION	
Utilization Patterns of Fosphenytoin and IV Phenytoin in the U.S., Years 2004 – 2009	***Grace Chai, Pharm.D.*** *Acting Drug Utilization Analyst Team Leader* *Division of Epidemiology, Office of Surveillance and Epidemiology (OSE), CDER, FDA*
Broad Profile of Adverse Events: Fosphenytoin Versus IV Phenytoin	***Jasmine Chen Gatti, M.D., M.A.*** *Medical Reviewer* *Division of Pharmacovigilance (DPV) I* *OSE, CDER, FDA*
Medication Errors Associated with Phenytoin and Fosphenytoin Use	***Anne Tobenkin, Pharm.D.*** *Safety Evaluator* *Division of Medical Error Prevention and Analysis (DMEPA), OSE, CDER, FDA*

Purple Glove Syndrome	***Andrew Fine, Pharm.D.*** *Safety Evaluator* *DPV I, OSE, CDER, FDA*
Purple Glove Syndrome Associated with Phenytoin or Fosphenytoin: Preliminary Report	***Simone P. Pinheiro, Sc.D., M.Sc., M.A.*** *Epidemiologist* *Division of Epidemiology, OSE, CDER, FDA*
Clarifying Questions	
BREAK	
INDUSTRY PRESENTATION	
Summary of Information about Purple Glove Syndrome in Association with Intravenous Administration of Phenytoin and Fosphenytoin	***Susan Welsh, M.B., Ch.B., B.Sc., F.F.P.M.*** *Vice President, Worldwide Safety Strategy* *Pfizer, Inc.*
Clarifying Questions	
GUEST SPEAKER PRESENTATION	
Point-Counterpoint: Should Intravenous Phenytoin Remain on the Market?	***William M. Coplin, M.D., F.C.C.M.*** *Associate Professor, Neurology & Neurological Surgery, Wayne State University* *Chief, Neurology and Medical Director Neurotrauma & Critical Care* *Detroit Receiving Hospital* ***Thomas P. Bleck, M.D., F.C.C.M.*** *Professor of Neurological Sciences, Neurosurgery, Medicine, and Anesthesiology* *Assistant Dean, Rush Medical College* *Associate Chief Medical Officer (Critical Care)* *Rush University Medical Center*
LUNCH	
Open Public Hearing	
Panel Discussion/Questions	
BREAK	
Panel Discussion/Questions	
Adjournment	

Questions to the Committee:

1. Does the committee agree that intravenous phenytoin causes Purple Glove Syndrome (PGS)? YES/NO/ABSTAIN

YES: 26 NO: 2 ABSTAIN: 1

Committee Discussion: *The majority of the committee felt that intravenous phenytoin causes Purple Glove Syndrome; the committee members who voted "NO" stated that they voted "NO" because PGS is not clearly defined.*

2. Does the committee believe there is adequate information to conclude that fosphenytoin causes PGS? YES/NO/ABSTAIN

YES: 11 NO: 18 ABSTAIN: 0

Committee Discussion: *The committee members who voted "NO" indicated that there is not adequate information to conclude causality.*

a. If the answer to question #2 is YES, does the committee believe there are differences in the risk of PGS between IV phenytoin and IV fosphenytoin? YES/NO/ABSTAIN

Committee Discussion: *The committee decided to not take a vote on question #2a. Some committee members stated that the occurrence of PGS of fosphenytoin seem to be lower and less severe since one would expect to see more case reports if it occurred more frequently. One member indicated that it is difficult to compare the risk of PGS between the two drug products since there is limited data..*

3. Is there adequate information to determine how often severe PGS (with clinically significant outcomes such as surgical intervention) occurs as opposed to the milder and moderate forms?

a. For phenytoin? YES/NO/ABSTAIN

YES: 9 NO: 18 ABSTAIN: 1 NO VOTE: 1

Committee Discussion: *It was noted for the record that one panel member had to step out of the room for an emergency phone call. The committee members who voted "NO" stated that there is not enough information to make this determination.*

b. For fosphenytoin? YES/NO/ABSTAIN

Committee Discussion: *The committee decided to not take a vote on question #3b.*

4. Can fosphenytoin be used interchangeably with IV phenytoin for:

a. All indications and therapeutic uses (e.g., arrhythmias)? YES/NO/ABSTAIN
b. In all settings of use (e.g., crash carts), considering the need for fosphenytoin refrigeration? YES/NO/ABSTAIN
c. For all age groups (e.g., pediatrics)? YES/NO/ABSTAIN
d. Are there settings where one agent is preferred over the other?
e. Are there settings where one of these agents should *not* be used?

Committee Discussion: *This question was skipped and was not discussed as the Agency received adequate information based on the day's discussions.*

5. Are there differences in risk for other clinically significant events with serious sequelae, (including cardiovascular events and/or hypotension, or medication errors) between IV phenytoin and fosphenytoin?

Committee Discussion: *This question was skipped and was not discussed as the Agency received adequate information based on the day's discussions.*

6. How does the frequency, the clinical phenotype (i.e., the characteristics of mild, moderate, and severe forms) and typical outcomes (i.e., spontaneous recovery, hospitalization, disability, amputation) of PGS compare to other safety concerns for IV phenytoin and/or fosphenytoin?

Committee Discussion: *This question was skipped and was not discussed as the Agency received adequate information based on the day's discussions.*

7. With the above in mind, would the committee:

    a. Request marketing suspension of phenytoin? YES/NO/ABSTAIN

YES: 0 NO: 29 ABSTAIN: 0

Committee Discussion: *The committee members unanimously agreed that the marketing of intravenous phenytoin should not be suspended. There was discussion that for non-neurological uses, there are alternatives to intravenous phenytoin; however, for neurological uses, there are no adequately studied alternatives to intravenous phenytoin except fosphenytoin.*

Additional question posed to the committee by the FDA: should the labeling of intravenous phenytoin be revised to indicate that fosphenytoin should be used first, before phenytoin.

Committee Discussion: *A few panel members agreed that the labeling of intravenous phenytoin should be revised to indicate that it should be used only if fosphenytoin is not available. The committee recommended that the labeling should be revised to encourage oral use of phenytoin whenever possible and that the risk of PGS may be greater with intravenous phenytoin than fosphenytoin. The majority of the committee did not recommend that the label should be revised to dictate the use of fosphenytoin first since the decision of which product to use should be dictated by the treating physician at the local level.*

b. Allow continued marketing of phenytoin without changes to the labeling? YES/NO/ABSTAIN

Committee Discussion: *The committee decided to not take a vote on question #7b since the general consensus amongst the committee members is that changes to the phenytoin labeling should be made.*

c. Allow continued marketing of phenytoin with revisions to the current label (e.g., the addition of contraindications for some populations, addition of more detailed administration instructions [e.g. catheter size, rate of infusion], a Boxed warning)? YES/NO/ABSTAIN

YES: 29 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee members discussed the following possible revisions to the labeling of intravenous phenytoin:*

- Consider use of fosphenytoin instead of intravenous phenytoin due to possible greater risk of PGS with intravenous phenytoin. This may not necessarily be a black box warning so as to not overstate the association, but the language should be strong enough to trigger a warning in computer ordering systems.
- The risk for PGS should be displayed more prominently in the label.
- Risk factors for PGS should be described in labeling.
- Highlight the risks associated with intravenous phenytoin and fosphenytoin as opposed to oral administration of phenytoin.
- Recommend a slower infusion rate for patients who are not actively convulsing since there are less cardiovascular adverse events with a slower infusion rate. However, in seizure emergencies, it can be given at a rate that is necessary up to the maximum recommended rate.
- Include a dosing table based on patient weight.
- Recommend changes in injection methods and dilutions that are similar to those used in large clinical series reporting no incidence of PGS.

d. Require any regulatory action for fosphenytoin? YES/NO/ABSTAIN

YES: 29 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee members recommended that the following actions should be taken regarding fosphenytoin:*

- Revise the label in such a manner as to reduce medication errors associated with prescribing fosphenytoin.
- Change the label to state that the risk of cardiovascular adverse events is the same for intravenous phenytoin and fosphenytoin.
- Revise the label to alert clinicians that PGS may be associated with fosphenytoin and state that cases of possible PGS have been reported to the FDA.

The meeting was adjourned at approximately 4:30 p.m.